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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/552,084 | 12/01/2006 | Robert L. Wolfert | DEX0478US.NP | 4146 |
| 32800 | 7590 | 10/17/2008 | EXAMINER | |
| LICATA & TYRRELL P.C. 66 E. MAIN STREET MARLTON, NJ 08053 | | | NIEBAUER, RONALD T | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1654 | |
| | | | NOTIFICATION DATE | DELIVERY MODE |
| | | | 10/17/2008 | ELECTRONIC |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

poreilly@licataandtyrrell.com

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/552,084 | WOLFERT ET AL. | |
| | Examiner | Art Unit | |
| | RONALD T. NIEBAUER | 1654 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 15 July 2008.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-11, 16, 18-21, 24, 25, 30-32 and 36-39 is/are pending in the application.

4a) Of the above claim(s) 3, 8, 9, 16, 18-21, 24, 25, 30-32, 37 and 38 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1-2, 4-7, 10-11, 36, 39 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

| | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Applicants amendments and arguments filed 7/15/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 12-15,17,22-23,26-29,33-35 have been cancelled.

Claims 36-39 have been added as new claims. As noted previously, applicant elected a patient disorder/patient population of hypertension. New claims 37-38 are drawn to non-elected species of patient disorder/patient population. Claims 3,8-9,16,18-21,24-25,30-32 were previously withdrawn.

Claims 3,8-9,16,18-21,24-25,30-32,37-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/31/08.

Although applicants request rejoinder of claims, no generic claim is allowable.

Claims 1-2,4-7,10-11,36,39 are under consideration.

Claim Rejections - 35 USC § 102

The below rejection is maintained for claims 1-2,4-7,11 and has been updated to include newly added claims 36,39.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2,4-7,11,36,39 are rejected under 35 U.S.C. 102(b) as being anticipated by Packard et al. (NEJM Oct 19 2000 v343 pages 1148-1155 as cited previously).

Packard teach that there are reports that C-reactive protein (CRP) levels are elevated in those at risk for coronary disease (page 1148 column 2 1st paragraph). Packard teach that lipoprotein-associated phospholipase A2 (Lp-PLA2, also known as platelet-activating factor acetylhydrolase) is a potential predictor of the risk of coronary heart disease (page 1148 column 2 2nd paragraph). Packard confirms that CRP and Lp-PLA2 are indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Thus the specific disease recited in claims 2,36 of the instant invention is met. Packard teach that the patient population includes patients with hypertension (table 1) thus meeting the limitation of the elected patient population. Packard teach that CRP and Lp-PLA2 were measured in aliquots of plasma collected from patients (page 1149 ‘measurements’ section 2nd paragraph) thus the sampling (which is a step of the measuring process) was done simultaneously thus meeting the limitations of claim 4 of the instant invention and the samples were from patients as recited in claim 39. Packard also teach that separate enzyme-linked immunoassays were performed for CRP and Lp-PLA2 (page 1149 ‘measurements’ section 2nd and 3rd paragraphs) thus the assaying (which is a step of the measuring process) was performed sequentially thus meeting the limitations of claim 5 of the instant invention. Packard teach that Lp-PLA2 mass was measured (page 1149 ‘measurements’ section 3rd paragraph) thus meeting the limitation of claim 11 of the instant invention. Packard

teach that quintile ranges (i.e. divided into 5 classes) were established for the variables (page 1149 ‘statistical analysis’ section 1st paragraph). Since there are 5 classes there are necessarily high and low levels as well as high, medium, and low levels as recited in claims 6-7 of the instant invention. It is noted that claims 6-7 recite ‘and a patient having both high CRP and high Lp-PLA2 levels is indicative of heightened risk of CVD’. However, such recitation does not require steps to be performed and do not limit the claim scope (see MPEP section 2111.04). Packard specifically teach a multivariate assessment on the risk of a coronary event (Table 5). As such, the models used the variables including CRP and Lp-PLA2 (i.e. a combination of risk factors). Packard confirms that CRP and Lp-PLA2 are both indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Taken together, Packard teach the limitations of claim 1 including measuring levels of Lp-PLA2 and CRP (page 1149 ‘measurements’ section 2nd paragraph), analyzing the risks (Table 5), and using the risks (page 1152 ‘discussion’ section 1st paragraph, Table 5) thus meeting the limitations of claim 1 of the instant invention.

Response to Arguments 102 rejection

Applicants argue that Packard does not teach all elements of the instant claimed invention. Applicants argue that Lp-PLA2 is taught as an independent predictor of coronary heart disease. Applicants argue that Packard teach models to assess the independent prognostic value of variables and that the variables as predictors of coronary events was assessed. Applicants argue that Packard teach multivariate assessment to determine the independence of the variables. Applicants argue that Packard does not teach use of the combined risks of Lp-PLA2 and CRP to assess the risk of CVD in a patient.

Applicant's arguments filed 7/15/08 have been fully considered but they are not persuasive.

Although applicants argue that Packard does not teach use of the combined risks of Lp-PLA2 and CRP to assess the risk of CVD in a patient, Packard confirms that CRP and Lp-PLA2 are both indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Table 5 is entitled ‘Multivariate assessment of the effect of inflammatory markers on the risk of a coronary event’. Thus one would recognize that the model assesses the risk of a coronary event. The Table 5 caption states that the model included the factors shown. In particular, both Model 1 and Model 2 teach C-reactive protein (CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2) as variables in the model. In column 2 of Table 5, Packard report risk values. Since Lp-PLA2 and CRP are risks (page 1152 ‘discussion’ section 1st paragraph) and are included in the models used in Table 5, the models which report risks necessarily use both Lp-PLA2 and CRP.

It is noted that claim 1 recites ‘using the combined risks to assess the risk’. Section 2111 of the MPEP states that the claims are to be given the broadest reasonable interpretation. In the instant case, the claims state an active step of ‘using the combined risks’. No special definition is provided for the word ‘combine’ in the instant specification, thus the term is given the broadest reasonable interpretation. Packard confirms that CRP and Lp-PLA2 are both indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Packard teach that a model is used to calculate risks and the model uses variables including Lp-PLA2 and CRP (Table 5). Thus the model uses a combination of risks. Further, no special definition is provided for the word ‘assess’. Thus the term is given the broadest reasonable interpretation. Table 5 is entitled

‘Multivariate assessment of the effect of inflammatory markers on the risk of a coronary event’.

As such, the model uses a combination of variables, including Lp-PLA2 and CRP to assess the risk. Thus, Packard meet the particular active step as claimed.

Applicants argue that Lp-PLA2 is taught as an independent predictor of coronary heart disease and that Packard teach multivariate assessment to determine the independence of the variables. First, it is noted that applicants acknowledge (page 15 lines 4-5) that a multivariate assessment of the variables, particularly Lp-PLA2 and CRP was undertaken by Packard. Table 5 is entitled ‘Multivariate assessment of the effect of inflammatory markers on the risk of a coronary event’, thus one would recognize that the assessment is an assessment on the risk of a coronary event as recited in the instant claims. Although Packard discuss other uses of the model (to assess the independent prognostic value of variables) and discuss the implications and analysis of the model, such alternate uses and analysis do not take away from the fact that the model was used. In other words, to perform the analysis or intended use Packard carry out active steps that meet the instant claim limitations. Since the active steps of the claims are taught by the prior art the claim limitations are necessarily met.

For these reasons and the reasons set forth previously, claims 1-2,4-7,11,36,39 are rejected under 35 U.S.C. 102(b)

Claim Rejections - 35 USC § 103

The below rejection is maintained for claims 1-2,4-7,10-11 and has been updated to include newly added claims 36,39.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2,4-7,10-11,36,39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Packard et al. (NEJM Oct 19 2000 v343 pages 1148-1155 as cited previously) and further in view of Rao et al. (US 2003/0120134 as cited previously).

As discussed above Packard teach that there are reports that C-reactive protein (CRP) levels are elevated in those at risk for coronary disease (page 1148 column 2 1st paragraph). Packard teach that lipoprotein-associated phospholipase A2 (Lp-PLA2, also known as platelet-activating factor acetylhydrolase) is a potential predictor of the risk of coronary heart disease (page 1148 column 2 2nd paragraph). Packard confirms that CRP and Lp-PLA2 are indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Thus the specific disease recited in claims 2,36 of the instant invention is met. Packard teach that the patient

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population includes patients with hypertension (table 1) thus meeting the limitation of the elected patient population. Packard teach that CRP and Lp-PLA2 were measured in aliquots of plasma collected from patients (page 1149 ‘measurements’ section 2nd paragraph) thus the sampling (which is a step of the measuring process) was done simultaneously thus meeting the limitations of claim 4 of the instant invention and the samples were from patients as recited in claim 39. Packard also teach that separate enzyme-linked immunoassays were performed for CRP and Lp-PLA2 (page 1149 ‘measurements’ section 2nd and 3rd paragraphs) thus the assaying (which is a step of the measuring process) was performed sequentially thus meeting the limitations of claim 5 of the instant invention. Packard teach that Lp-PLA2 mass was measured (page 1149 ‘measurements’ section 3rd paragraph) thus meeting the limitation of claim 11 of the instant invention. Packard teach that quintile ranges (i.e. divided into 5 classes) were established for the variables (page 1140 ‘statistical analysis’ section 1st paragraph). Since there are 5 classes there are necessarily high and low levels as well as high, medium, and low levels as recited in claims 6-7 of the instant invention. It is noted that claims 6-7 recite ‘and a patient having both high CRP and high Lp-PLA2 levels is indicative of heightened risk of CVD’. However, such recitation does not require steps to be performed and do not limit the claim scope (see MPEP section 2111.04). Packard specifically teach a multivariate assessment on the risk of a coronary event (Table 5). As such, the models used the variables including CRP and Lp-PLA2 (i.e. a combination of risk factors). Packard confirms that CRP and Lp-PLA2 are both indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Taken together, Packard teach the limitations of claim 1 including measuring levels of Lp-PLA2 and CRP (page 1149 ‘measurements’ section 2nd paragraph), analyzing the risks (Table 5), and using the risks (page

1152 ‘discussion’ section 1st paragraph, Table 5) thus meeting the limitations of claim 1 of the instant invention.

Packard does not expressly teach the use of ATP III guidelines as recited in claim 10.

Rao et al. teach systems and methods for screening for coronary heart disease (abstract). Rao teach that patients are assessed for risk for coronary heart disease based on factors (section 0032). Rao specifically teach that the Adult Treatment Panel (ATP III) has produced guidelines for risk. Rao teach the use of the guidelines in the system for screening for coronary heart disease.

Both Packard and Rao teach methods for assessing risk of coronary heart disease. Since there is evidence that cardiovascular risk and disease is under-treated (Rao section 0005) one would be motivated to use various methods and combinations of methods to assess risk of coronary heart disease. In particular one would be motivated to use the CRP and Lp-PLA2 risks and additionally use the ATP III guidelines as taught by Rao with the method of Packard thus meeting the limitations of the claims of the instant invention. It is noted that it is obvious to combine compositions each of which is taught by the prior art to be useful for the same purpose (see MPEP section 2144.06). Likewise is it obvious to combine risks (such as those associated with CRP, Lp-PLA2, and ATP III guidelines) for the purpose of assessing the risk of coronary heart disease.

It has been recently held that “Neither §103’s enactment nor *Graham’s* analysis disturbed the Court’s earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art.” KSR v. Teleflex, 550 U.S. ___, 82 USPQ2d

1385, 1389 (2007). The KSR court stated that “a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” KSR at 1389.

Furthermore, The KSR court concluded that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in *KSR*

When there is motivation

"to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

In the instant case all the claimed elements were known in the art as discussed above and one skilled in the art could have combined the elements by known methods and the combination would have yielded predictable results. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Response to Arguments 103 rejection

Applicants argue that the references do not teach using the combined risks to assess the risk of CVD in a patient. Applicants argue that the references do not teach or suggest all limitations of the claims. Applicants argue that when considering the obviousness of a combination that the instant invention is an improvement of more than any predictable use set forth by the prior art.

Applicant's arguments filed 7/15/08 have been fully considered but they are not persuasive.

As discussed above, although applicants argue that Packard does not teach use of the combined risks of Lp-PLA2 and CRP to assess the risk of CVD in a patient, Packard confirms that CRP and Lp-PLA2 are both indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Table 5 is entitled ‘Multivariate assessment of the effect of inflammatory markers on the risk of a coronary event’. Thus one would recognize that the model assesses the risk of a coronary event. The Table 5 caption states that the model included the factors shown. In particular, both Model 1 and Model 2 teach C-reactive protein (CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2) as variables in the model. In column 2 of Table 5, Packard report risk values. Since Lp-PLA2 and CRP are risks (page 1152 ‘discussion’ section 1st paragraph) and are included in the models used in Table 5, the models which report risks necessarily use both Lp-PLA2 and CRP.

It is noted that claim 1 recites ‘using the combined risks to assess the risk’. Section 2111 of the MPEP states that the claims are to be given the broadest reasonable interpretation. In the instant case, the claims state an active step of ‘using the combined risks’. No special definition is provided for the word ‘combine’ in the instant specification, thus the term is given the broadest reasonable interpretation. Packard confirms that CRP and Lp-PLA2 are both indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Packard teach that a model is used to calculate risks and the model uses variables including Lp-PLA2 and CRP (Table 5). Thus the model uses a combination of risks. Further, no special definition is provided for the word ‘assess’. Thus the term is given the broadest reasonable interpretation. Table 5 is entitled

‘Multivariate assessment of the effect of inflammatory markers on the risk of a coronary event’.

As such, the model uses a combination of variables, including Lp-PLA2 and CRP to assess the risk. Thus, Packard meet the particular active step as claimed.

Applicants argue that Lp-PLA2 is taught as an independent predictor of coronary heart disease and that Packard teach multivariate assessment to determine the independence of the variables. First, it is noted that applicants acknowledge (page 15 lines 4-5) that a multivariate assessment of the variables, particularly Lp-PLA2 and CRP was undertaken by Packard. Table 5 is entitled ‘Multivariate assessment of the effect of inflammatory markers on the risk of a coronary event’, thus one would recognize that the assessment is an assessment on the risk of a coronary event as recited in the instant claims. Although Packard discuss other uses of the model (to assess the independent prognostic value of variables) and discuss the implications and analysis of the model, such alternate uses and analysis do not take away from the fact that the model was used. In other words, to perform the analysis or intended use Packard carry out active steps that meet the instant claim limitations. Since the active steps of the claims are taught by the prior art the claim limitations are necessarily met.

Although applicants argue that the references do not reach or suggest all of the claim limitations, it is noted that as discussed above, all the claim limitations are met. In particular, Packard confirms that CRP and Lp-PLA2 are indicators of risk of coronary heart disease (page 1152 ‘discussion’ section 1st paragraph). Rao teach that patients are assessed for risk for coronary heart disease based on factors (section 0032). Rao specifically teach that the Adult Treatment Panel (ATP III) has produced guidelines for risk. Rao teach the use of the guidelines in the system for screening for coronary heart disease. Since the prior art recognize the use of

CRP and Lp-PLA2 and the ATP III guidelines for assessing risk of coronary heart disease, the idea of combining the risks logically flows from their having been individually been taught in the prior art.

Although applicants argue that the instant invention is an improvement of more than any predictable use set forth by the prior art, section 716.02(b) of the MPEP states that burden is on the applicant to establish that results are unexpected and significant. In the instant case, applicants make a general assertion about the instantly claimed invention. However, it is unclear what specific data applicant is referencing and it is unclear what specific comparison to the prior art that applicant is making. Further, it is unclear how or why the instant invention is an improvement of more than any predictable use set forth by the prior art.

For these reasons and the reasons set forth previously, claims 1-2,4-7,10-11,36,39 are rejected under 35 U.S.C. 103(a).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/Ronald T Niebauer/
Examiner, Art Unit 1654